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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/579,981	01/07/2007	Rocky Marc Cranenburgh	CARP-0123	3679

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EXAMINER	
PITRAK, JENNIFER S	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
03/17/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/579,981	CRANENBURGH, ROCKY MARC	
	Examiner	Art Unit	
	JENNIFER PITRAK	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,10,11,13-41,44,45 and 72* is/are pending in the application.

4a) Of the above claim(s) *18,19,21-26,30-35,38-40,44,45 and 72* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,10,11,13-17,20,27-29,36,37 and 41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *07/26/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Sequence Compliance Notice*.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-11, 13-27, and 41 in the reply filed on 01/11/2008 is acknowledged. Applicant's election with traverse of the species *E. coli*, and a chromosomal gene encoding *lacI* in the reply filed on 01/11/2008 is acknowledged. The traversal is on the ground(s) that the subject matter is patentably distinct from the prior art and that the special technical feature is included in all of the groups. This is not found persuasive because the special technical feature, antisense inhibition of a target gene, is taught by Shohat, *et al.* as described on pages 2-3 of the Restriction Requirement mailed 09/14/2007, and thus does not make a contribution over the prior art. The requirement is still deemed proper and is therefore made FINAL.

Claims 38-40, 44, 45, and 72 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 01/11/2008.

Claims 18, 19, 21-26, 30-35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 01/11/2008, for the same reasons provided for the restriction requirement.

Applicant has amended claims 1, 10, 11, 36, and 37. Applicant has cancelled claims 4-9, 12, 42, 43, 46-71, and 73. **Claims 1-3, 10, 11, 13-17, 20, 27-29, 36, 37, and 41 are under examination.**

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. To be considered fully responsive, any reply to this action must address these deficiencies, as this requirement will not be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 36 and 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 36 and 37 recite the limitation "the regulatory sequence-chromosomal gene fusion". There is insufficient antecedent basis for this limitation in the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 10, 11, 13-17, 20, 27-29, 36, 37, and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morsey (WO97/14805, item 4 on IDS filed 07/26/2007), Galen, *et al.*(1999, Infection and Immunity, item 30 on IDS filed 07/26/2007), and del Solar, *et al.*(1998, Microbiol. and Molec. Biol. Rev., item 24 on IDS filed 07/26/2007) as evidenced by Hu & Davidson (1987, Cell v.48:555-566).

Deleted: Bujard, *et al.* (2000, U.S. Patent 6,136,954) and

The claims are to a transformed host cell comprising 1) a chromosomal gene that inhibits cell growth, wherein the chromosomal gene is operably linked to a regulatory sequence and 2) a plasmid comprising an origin of replication encoding an antisense sequence that binds to the mRNA transcribed from the regulatory sequence and inhibits action of the chromosomal gene, thereby permitting cell growth (claim 1). The claims are further to the transformed host cell wherein the plasmid comprises a cloning site for insertion of a gene of interest (claim 2) and further comprising a gene of interest (claim 3). Claims 13-17 and 20 are to the cell of claim 1 wherein the cell is cultured *in vitro,* is attenuated, and is an *E. coli* cell. Claims 27-29 are to the host cell of claim 1 wherein the inhibitory chromosomal gene encodes the *lacI* repressor that inhibits a second chromosomal gene operatively linked to a *lac* operator and promoter. Claims 36 and 37 are to the host cell of claim 1 wherein the chromosomal gene is under the control of a

constitutive or inducible promoter. Claim 41 is to the host cell of claim 1 in a pharmaceutical carrier.

Morsey teaches a culture (*in vitro*) system in which bacterial cells, including attenuated *E. coli* cells, are employed wherein the bacterial cell chromosome is irreversibly modified to effect production of a substance toxic (inhibitory to cell growth) to the bacterial cells, wherein the bacterial cells contain plasmids that produce a substance that inactivates the toxic substance (p.6, lines 20-28, claims 1 and 2, Figures depict attenuated *E. coli* strains). Claim 2 of Morsey's application specifies that the first substance is the product of the *hok* gene (toxin) and the second substance is the product of the *sok* gene (antisense mRNA antisense to the *hok* sequence), which, as taught by Galen, *et al.* is a postsegregational killing system in which the *sok* RNA inhibits translation of *hok* mRNA (Galen p.6425, first paragraph). Morsey further claims the above-described plasmid wherein the plasmid further includes foreign DNA for expression in eukaryotic cells (a cloned gene of interest) and claims a method comprising administering the bacterial cells of the invention to a host (pharmaceutical composition). Morsey also claims a culture system wherein the host chromosome is modified such that the cell is incapable of producing or uptaking (using) an essential metabolite and wherein the plasmid restores the ability to produce or uptake the metabolite (claims 7 and 10). Morsey does not teach that the antisense sequence is transcribed from the plasmid origin of replication nor does Morsey teach the RNA I or RNA II sequences for use as the antisense sequence. Morsey does not teach the cell-inhibitory gene as the *lacI* repressor, wherein the repressor inhibits expression of a *lac* operator/promoter-regulated essential gene.

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Deleted:, which is described by Galen, *et al.* as follows

Deleted: (p.6425, first paragraph).¶
The approach is based on the use of the naturally occurring hok-sok postsegregational killing system residing on the R factor pR1 (19, 20). The hok-sok system is a two-component toxin-antitoxin system in which hok encodes a lethal poreforming Hok protein. Synthesis of Hok is blocked by hybridization of a small antisense sok mRNA to hok mRNA, preventing translation and synthesis of Hok. However, sok mRNA is highly susceptible to degradation by nucleases, and its protective intracellular concentration must be maintained by constitutive transcription from resident plasmids carrying hok-sok. Therefore, bacteria that spontaneously lose such plasmids are postsegregationally killed because existing levels of the protective sok mRNA rapidly drop and levels of the more stable toxin-encoding hok mRNA quickly lead to Hok synthesis and cell death.

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¶

Deleted: Galen describes the plasmid system as useful for enhancing expression plasmid stability (abstract).

Comment [T1]: I'm a little unclear on what Galen is cited for. Is it just to show that hok/sok is a toxin-antitoxin system? If this is the case, I would rearrange the text a bit for clarity, right now you're discussing Morsey, then Galen, then Morsey. I would move Galen to either its own paragraph or the end of the Morsey paragraph. Also, you apparently rely on Bujard only to teach that the lac repressor regulates expression and then cite Hu to demonstrate the same thing. Do you need to cite both? It seems like you if you really need Hu you don't necessarily need Bujard?

Right.

del Solar, *et al.* teach that all plasmid origins of replication produce transcribed RNA and that some of the transcribed RNA is used directly for plasmid replication, as in the case of the ColE1 plasmid's antisense-mediated replication system comprising RNA I and RNA II, and some transcribed RNA is translated to a protein that is required for plasmid replication (p.435 and Figure 1). del Solar teaches that RNA I is transcribed from a constitutive promoter (p.453, latter half of the first column).

Hu & Davidson teach the use of the *lac* operator-repressor system as useful for regulating gene expression. Specifically, the abstract recites the following:

> We have investigated the use of the Escherichia coli lac operator-repressor system to regulate expression of transfected genes in mammalian cells. We show that lac repressor produced in mouse L cells by transfection of a lacI expression vector blocks transcription of an MSV-CAT fusion gene when the lac operator is inserted at any one of the following sites within the promoter region: between the initiation codon (ATG) and the transcription start site; between the transcription start and TATA box regions; or upstream of the TATA box region. This last result suggests that the repressor may prevent protein-protein interactions involved in transcription activation. The inducer IPTG causes a marked derepression of CAT expression. The lac repressor-operator complex may be useful as an on/off "switch" in the regulation of gene expression for gene transfer experiments.

Deleted: Bujard, *et al.* teaches that the *lac* repressor/inducer system can be used to regulate gene expression. Column 1, lines 50-65 explain that the Lac repressor (lacR)/operator/inducer system of *E. coli* has been used to regulate gene expression by preventing transcription initiation by properly placed lac operators at promoter sites. Bujard, *et al.*, cite Hu and Davidson, who teach the following (abstract): ¶

It would have been obvious to one skilled in the art at the time of the instant application to make a transformed host cell comprising (1) a chromosomal toxic gene linked to either the RNA I or the RNA II sequence and (2) a plasmid that encodes the complementary RNA II or RNA I, respectively, from the origin of replication for the purpose of enhancing the stability of an expression plasmid because the use of such toxin-antitoxin systems involving RNA-RNA binding were known, such as the *hok/sok* system taught by Morsey and Galen, *et al.* and because RNA I and RNA II comprise a known RNA-RNA regulatory system, therefore use of the RNA I/RNA II system is a matter of substitution of one known element for another that performs the same function. It further would have been obvious to the *lac* repressor/inducer system taught by

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Hu and Davidson to regulate the chromosomal inhibitory gene, because it was well-known at the time of filing as an IPTG-inducible expression system. Thus, the claims would have been obvious at the time of filing of the instant application.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JENNIFER PITRAK whose telephone number is (571)270-3061. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Pitrak, PhD
Examiner
Art Unit 1635

/Tracy Vivlemore/
Examiner, Art Unit 1635

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